IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

re application of:	Examiner: Bunner, Bridget E.
Kevin P. BAKER, *et al.*	Art Unit: 1647
Application Serial No. 10/015,394	Confirmation No: 9887
Filed: December 11, 2001	Attorney's Docket No. 39780-2830 P1C41
For: **ANTI-PRO1760 ANTIBODIES**	**Customer No. 35489**

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On April 8, 2005, the Examiner made a Final Rejection to pending Claims 28-32. A Notice of Appeal was filed on September 8, 2005, and Appellants' Appeal Brief was filed November 8, 2005.

An Examiner's Answer was mailed on February 22, 2005. The following constitutes Appellants' Reply Brief in response to the Examiner's Answer. This Reply Brief is accompanied by a Request for Oral Hearing.

ARGUMENTS

Claim Rejections Under 35 U.S.C. §101

Claims 28-32 stand rejected under 35 U.S.C. §101 as allegedly lacking either a credible, specific and substantial asserted utility or a well established utility.

The Examiner asserts that the results of the adipocyte glucose/FFA uptake assay, showing that PRO1760 tested positive as an inhibitor of glucose/FFA uptake in adipocyte cells, do not provide utility for the PRO1760 polypeptide or the claimed antibodies that bind it. In support of this assertion, the Examiner makes the following arguments:

(1) PRO1760 is an inhibitor of glucose uptake and thus would not have utility in the treatment of disorders such as obesity, diabetes, and hyper- or hypo-insulinemia because it is desirable to stimulate glucose uptake in these conditions;

(2) inhibitors of PRO1760 would not have utility because the instant specification does not teach that the PRO1760 polypeptide is correlated with any specific disorders;

(3) the specification does not teach that PRO1760 is involved in leptin regulation or that PRO1760 could be used as a pharmacological tool for investigation of leptin regulation; and

(4) the proposed use of the PRO1760 polypeptide as a potential therapeutic tool to investigate leptin regulation is simply a starting point for further research and investigation into potential practical uses of the polypeptides.

The Examiner's arguments will be addressed in the order they are listed above.

The Examiner asserts that "the skilled artisan would not expect PRO1760, which inhibits glucose uptake as asserted by the specification, to be beneficial to such disorders as obesity, diabetes, and hyper- or hypo-insulinemia, because in these conditions little or no glucose is entering the cells to begin with," and that therefore "one would expect the PRO1760 polypeptide to *exacerbate* the condition." (Page 7 of the Examiner's Answer; see also pages 11-12, 15).

Appellants respectfully point out that the fact that PRO1760 inhibits glucose uptake does not make it useless in such treatment. One of skill in the art would readily understand that a protein which inhibits glucose uptake into adipocytes is a useful therapeutic target, since blocking the function of this protein would decrease the inhibition, and thus increase glucose uptake into adipocytes. Accordingly, the PRO1760 polypeptide and inhibitors thereto (such as the claimed antibodies) are useful in the therapeutic treatment of disorders wherein stimulation of

glucose uptake by adipocytes is expected to be therapeutically effective, such as obesity, diabetes, and hyper- or hypo-insulinemia.

The Examiner asserts that inhibitors of PRO1760 would lack utility because "the instant specification does not teach that the PRO1760 polypeptide is even correlated with a disorder, particularly obesity, diabetes, and hyper- or hypo-insulinemia." The Examiner further notes that "the specification does not teach PRO1760 protein expression levels in normal or diseased subjects" and concludes that "[i]n order for a polypeptide to be useful, as asserted, for diagnosis or treatment of a disease, there must be a well-established or disclosed correlation or relationship between the polypeptide and a disease or disorder." (Page 8 of the Examiner's Answer; see also pages 12, 15-16).

Appellants respectfully submit that the facts of the instant situation are similar to those in as *Nelson v. Bowler,*[1] in which the claims at issue were directed to 16-phenoxy prostaglandins which showed activity in stimulation of smooth muscle tissue from gerbil colons and in modulation of blood pressure in rats. Although Nelson admitted that antifertility activity such as luteolysis was not proven by these tests, the Court concluded nonetheless that "tests evidencing pharmacological activity may manifest a practical utility **even though they may not establish a specific therapeutic use**"[2] (emphasis added). The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[3] Accordingly, it is not necessary to demonstrate that PRO1760 or its inhibitors have a specific therapeutic use in the treatment of a particular disease. The disclosure that PRO1760 has a pharmacological activity, regulation of glucose and FFA transport in adipocytes, is sufficient to demonstrate utility for PRO1760.

Appellants also point out that Mueller *et al.* (1998) disclose that inhibitors of adipocyte glucose uptake, including 2-DG, phloretin, and cytocholasin B, inhibit leptin gene expression and leptin secretion from adipocytes. It was known in the art at the time of filing that leptin is

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[1] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[2] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[3] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

involved in the regulation of food intake, energy expenditure, and body fat stores, and that leptin decreases after fasting or caloric restriction and increases a number of hours after refeeding. (Mueller *et al.* (1998), p. 551, col. 1). One of skill in the art would therefore have understood that agents capable of modulating leptin regulation would be useful in investigations regarding the treatment of obesity. Similarly, PRO1760, as an inhibitor of adipocyte glucose uptake, would be useful as a pharmacological tool for investigation of leptin regulation and obesity, in the same way as agents already known and used in the art such as 2-DG, phloretin, and cytocholasin B.

The Examiner asserts that the specification "does not teach that PRO1760 is involved in leptin regulation or that PRO1760 could be used as a pharmacological tool for investigation of leptin regulation." (Page 8 of the Examiner's Answer; see also page 13).

As discussed above, Mueller *et al.* (1998) demonstrated that insulin-induced increases in leptin secretion were more closely related to the amount of glucose taken up by the adipocytes than to the insulin concentration, suggesting a role for glucose transport and/or metabolism in regulating leptin secretion. Mueller *et al.* further demonstrated that both metformin and vanadium increased glucose uptake and inhibited leptin secretion from cultured adipocytes. (Muller *et al.*; 2000). Thus it was known in the art at the time of filing that molecules which regulated glucose uptake by adipocytes also, as a consequence, regulated leptin secretion. The specification clearly discloses that PRO1760 is an inhibitor of glucose uptake into adipocyte cells; thus one of ordinary skill in the art would understand that as a necessary consequence of regulating adipocyte glucose uptake, PRO1760 would also affect leptin secretion. Thus PRO1760 would be useful as a pharmacological tool for investigation of leptin regulation and the disorders with which it is associated, such as obesity.

The Examiner asserts that "the proposed use of the claimed PRO1760 polypeptides as a potential therapeutic tool to investigate leptin regulation is simply a starting point for further research and investigation into potential practical uses of the polypeptides." (Page 8 of the Examiner's Answer; see also page 13). In support of this assertion, the Examiner cites Mueller 2000 to the effect that "[f]urther research, including examination of the potential roles of glucose oxidation and lipogenesis, needs to be conducted to determine the precise biochemical and molecular mechanisms by which glucose metabolism regulates leptin production." (Page 13 of the Examiner's Answer). Appellants respectfully point out that the "further research" described in

Mueller 2000 is not directed towards finding practical utilities for glucose uptake inhibitors such as 2-DG, phloretin, cytocholasin B, or PRO1760. Rather, the further research is directed towards understanding the mechanisms through which glucose regulates leptin production. In order to conduct such research, it is necessary to have a means of reliably controlling the key variable of how much glucose enters the leptin-secreting adipocyte cells. Glucose uptake inhibitors such as PRO1760 have practical utility in enabling researchers to conduct such experiments, by providing a method of controlling the amount of glucose taken up by the adipocytes.

The Examiner asserts that "[w]hereas a scale or a microarray or a gas chromatograph has patentable utility as a research tool, the objects being evaluated with these research tools do not necessarily have patentable utility." (Page 9 of the Examiner's Answer; see also page 19). Appellants respectfully point out that the proposed use of PRO1760 (and the claimed antibodies that bind it) is not as an object of research. The research in which PRO1760 is involved is the study of glucose metabolism and leptin regulation. PRO1760 is useful in such research because it provides researchers with a tool that enables them to control the amount of glucose taken up by leptin-secreting adipocyte cells.

Appellants have previously pointed out in their Appeal Brief that the Patent Office routinely issues patents for inventions whose only use is to facilitate research, such as the DNA ligases of Example 10 of the Revised Interim Utility Guidelines Training Materials. The Examiner asserts that "DNA ligases have a well-established utility in the art based on this class of proteins' ability to ligate DNA. Also, the literature discloses many DNA ligases which have been fully characterized at the structural and functional levels." (Page 19 of the instant Office Action). Appellants respectfully submit that the family of glucose uptake inhibitors, including, for example, 2-DG, phloretin and cytocholasin B, also have a well-established utility in the art, as discussed above. As evidenced by this list of glucose uptake inhibitors, it is clear that the literature discloses many members of the family which have been structurally and functionally characterized. Thus the family of glucose uptake inhibitors meets the same standards as the family of DNA ligases.

As the Patent Office acknowledges, there are many research situations in which researchers need tools for ligating a DNA; hence DNA ligases have utility. It is equally true that there are research situations in which researchers need tools for controlling the amount of glucose

uptake by adipocyte cells; hence molecules which inhibit glucose uptake are useful. The Patent Office continues to incorrectly assert that Appellants have proposed using PRO1760 as an object of research, while not addressing Appellants' evidence that PRO1760 has a specific activity as a glucose uptake inhibitor, and that molecules with this activity have known uses as research tools.

Finally, the Examiner asserts that "the PRO1760 polypeptide, and the claimed antibodies that bind it, are not disclosed as having an activity that can be specifically useful," and concludes that "if the specification discloses nothing specific and substantial about the PRO1760 polypeptide, therefore both the polypeptide and its inhibitory molecules (e.g., antibodies) have no patentable utility." (Page 18 of the Examiner's Answer).

Appellants note that the specificity requirement is not an onerous one. The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed.[4] Such is clearly not the case here. The asserted utility for the PRO1760 polypeptide is not based upon vague "biological properties," but a specific activity, inhibition of glucose uptake by adipocytes. This activity has already been demonstrated, as shown in Example 149 of the specification. As demonstrated by publications such as Mueller (2000) and references 28-30 cited therein, molecules which inhibit glucose uptake by adipocytes have a well-established use as research tools. Accordingly, PRO1760 has a specific utility in the study of disorders associated with altered glucose uptake by adipocytes, such as diabetes, obesity, and hyper- and hypo-insulinemia.

Appellants further note that the subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner v. Mason*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use.[5]

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[4] *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

[5] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

As discussed above, beneficial uses beyond studying the claimed invention itself have been demonstrated for PRO1760, in particular, the study of disorders associated with altered glucose uptake by adipocytes, such as diabetes, obesity, and hyper- and hypo-insulinemia. Accordingly, the PRO1760 polypeptide has a specific and substantial utility.

The case law has clearly established that Appellants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[6] The Examiner has the initial burden that Appellants' claims of usefulness are not believable on their face.[7] In general, an Appellant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[8], [9] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[10] gives the following instruction to patent examiners: "If the Appellant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

As discussed above and in Appellants' Brief, the instant specification and the known art at the time of filing clearly demonstrate that PRO1760 has an activity, inhibition of glucose uptake by adipocytes, that is useful for practical purposes. In particular, PRO1760 has at least two different types of practical utilities. PRO1760 is useful as a target in screening assays to identify agents that increase glucose uptake, and could be used therapeutically in the treatment of diseases such as disorders such as obesity, diabetes, and hyper- or hypo-insulinemia. PRO1760 is also useful in the investigation of glucose uptake and the mechanisms of diseases related to glucose uptake, such as obesity, diabetes, and hyper- or hypo-insulinemia.

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[6] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[7] *Ibid.*

[8] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[9] *See also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (C.C.P.A. 1977).

[10] M.P.E.P. §2107 II (B)(1).

Accordingly, for at least the above reasons, the results of the adipocyte glucose/FFA uptake assay provide a specific, substantial and credible utility for the PRO1760 polypeptide and the claimed antibodies that bind it.

Claim Rejections Under 35 U.S.C. §112, First Paragraph - Enablement

Claims 28-32 stand rejected under 35 U.S.C. §112, first paragraph, for essentially the same reasons as discussed above. Appellants respectfully submit that as described above, the PRO1760 polypeptide and the claimed antibodies that bind it have utility in the treatment of disorders for which modulation of glucose uptake by adipocytes would be beneficial, such as obesity, diabetes, and hyper- or hypo-insulinemia, or as pharmacological tools for the study of these diseases and conditions, and based on such a utility, one of skill in the art would know exactly how to use the claimed antibodies without undue experimentation.

Accordingly, Appellants respectfully request reconsideration and reversal of the enablement rejection of Claims 28-32 under 35 U.S.C. §112, first paragraph.

CONCLUSION

For the reasons given above, Appellants submit that the adipocyte glucose/FFA uptake assay disclosed in Example 149 of the specification provides at least one asserted specific and substantial patentable utility for the PRO1760 polypeptide and the claimed antibodies that bind it, and that one of ordinary skill in the art would accept this asserted utility as credible and would understand how to make and use the claimed antibodies. Therefore, claims 28-32 meet the requirements of 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

Accordingly, reversal of all the rejections of Claims 28-32 is respectfully requested.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C41**).

Respectfully submitted,

Date: April 21, 2006

By: _____
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